Procalcitonin as marker of the severity of sepsis in critically ill children

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ABSTRACT

Objective: To assess the role of procalcitonin (PCT) in the diagnosis and prognosis in children with sepsis. **Design:** Prospective, observational study. **Setting:** Tertiary care center in South India. **Participants:** Children, 1 month to 15 years of age, admitted with the diagnosis of sepsis excluding children with chronic systemic/inflammatory disease, degenerative neurologic disease, primary/acquired immune deficiency, on steroids and children who had trauma/burns. **Intervention:** None. **Main Outcome Measures:** Serum PCT levels, grades of sepsis and mortality. **Results:** Respiratory tract infection was the most common source of sepsis (71%). Of the 53 patients studied, PCT was >2 ng/ml in 42 (79.2%) patients. Mean PCT values were 9.63, 17.72, and 84.68 ng/ml in sepsis, severe sepsis, and septic shock, respectively. PCT was found to be 86.36% sensitive, 55.56% specific with a positive predictive value (PPV) of 90.48, and negative predictive value of 45.45. 79.2% of patients in the study were discharged and 18.9% died. PCT levels were high in children who died subsequently. **Conclusions:** There is a positive association between PCT levels and the severity of sepsis as reflected by high sensitivity and PPV. High PCT levels also indicate increased chances of mortality.

Key words: *Procalcitonin, Sepsis, Septic shock, Severe sepsis, Systemic inflammatory response syndrome*

Sepsis in the pediatric intensive care unit (PICU) has always been challenging to the treating physician. Early institution of an appropriate antimicrobial regimen in infected patients is associated with a better outcome, and hence, early diagnosis is vital. Clinical examination is not always reliable in distinguishing between patients with bacterial sepsis and systemic inflammatory response syndrome (SIRS). This along with the lack of specific early markers of infection may be responsible for withholding or delaying antimicrobial treatment in critically ill patients.

There is a need for an effective and accurate biochemical marker to support or exclude the diagnosis of infection. Procalcitonin (PCT) has emerged as a more reliable marker to differentiate SIRS from systemic inflammation than C-reactive protein (CRP), interleukin-1 (IL-1) in adult studies [1-4]. PCT has also been a more reliable marker in early neonatal sepsis within 12 h of life than either CRP or IL-6 [5]. However, conflicting data exists about the role of PCT in the diagnosis of sepsis in children. Hence, this study was undertaken to study the serum PCT levels in children with the diagnosis of sepsis and to assess its correlation with the severity of the disease.

METHODOLOGY

This was a prospective, observational study, enrolling children aged 1 month to 15 years, admitted to M. S. Ramaiah Memorial Hospital with suspicion of sepsis over 1 year. After obtaining approval from the Hospital Ethics Committee and informed consent from parents, all consecutive patients admitted to hospital with suspicion of sepsis were enrolled and observed till discharge, transfer, or death.

The sample size was calculated for 95% confidence interval, 80% power of the study, and came to 48 cases. Children with chronic systemic/inflammatory disease, degenerative neurologic disease, primary/acquired immune deficiency, on steroids and children who had an illness for more than 48 h and on antibiotics or recently vaccinated, children who had trauma/burns were excluded. On admission, detailed history and clinical examination were done, and the children were assigned to the various groups of the sepsis classification, *viz*., SIRS, sepsis, severe sepsis, and septic shock on admission [6]. SIRS, sepsis, and septic shock were defined according to the criteria established by the Consensus on International Sepsis Definitions Conference, 2001 [6].

The initial diagnosis on admission was used to assign patients to each of the study groups. Complete blood counts, blood culture, serum CRP, and serum PCT were done on admission for all cases. Other investigations, such as arterial blood gases, urine microscopy, specimen culture, serum electrolytes, renal function tests, liver function tests, coagulation profile,

and chest X-ray, were done as per requirement in each case. Patients were treated as per the PICU protocol. The PCT assay was done by immunoluminometric assay (BRAHMS PCT LIA; Neuendorfstr) and was interpreted as follows: levels <0.5 ng/ml indicating probable local infection and not sepsis, levels >0.5 and <2 ng/ml as possible systemic infection, >2 and <10 ng/ml as likely systemic infection, and >10 ng/ml as high likelihood of severe sepsis or septic shock [7]. Outcome parameters were the length of stay in PICU and mortality.

Descriptive statistical analysis was carried out, and significance was assessed at 5% level of significance. Student's t-test (two-tailed, independent) was used to find the significance of study parameters on a continuous scale between two groups-intergroup analysis. Chi-square or Fisher exact test was used to find the significance of study parameters on a categorical scale between two or more groups, and Pearson's coefficient was used to find the correlation of PCT with CRP.

RESULTS

A total of 62 patients fulfilled the inclusion criteria; of which, 9 patients were excluded from the study due to earlier antibiotic use in 8 cases, and diagnosis of degenerative disease in one case. Of the 53 patients (54.5% males) studied, 9 (16.9%) cases were categorized as SIRS, 14 (26.4%) as sepsis, 8 (15.1%) as severe sepsis, and 22 (41.5%) as septic shock. 34 (64.2%) were <2 years, 10 (18.9%) aged 2-5 years, 5 (9.4%) aged 5-10 years, and 4 (7.5%) were more than 10 years.

The common clinical presentations were fever (96.2%), cough (90.6%), loose stools (26.4%), decreased activity and feeding (86.8%), rapid breathing (79.2%), bleeding manifestations (11.3%), and vomiting (7.5%). The primary focus of infection was the respiratory system (71.6%), followed by gastrointestinal and central nervous system (7.5%), and urinary tract infection and cellulitis (1.88%).

Out of 53 patients, 12 patients had positive blood culture (*Staphylococcus aureus* - 6, *Klebsiella* - 2, *Escherichia coli* - 1, *Staphylococcus pneumonia* - 1, *Staphylococcus typhi* - 1, *Pseudomonas* - 1). 7 patients (13.2%) had leukopenia, 16 (30.2%) had normal counts, and 30 (56.6%) had leukocytosis. 20 patients had a platelet count of <1 lakh while 33 patients had a platelet count of more than 1 lakh. None of the hematological parameters (hemoglobin, total leukocyte, and neutrophil count) were statistically associated with a diagnosis of sepsis or with PCT levels.

About 42 (79.2%) patients had values of PCT >2 ng/ml ($p<0.05$) as shown in Table 1. The mean values of serum PCT in the sepsis, severe sepsis, and septic shock groups were 9.63, 17.72, and 84.68 ng/ml, respectively. Mean PCT levels were significantly higher in children with septic shock than in sepsis ($p=0.013$).

The mean values of serum CRP in sepsis, severe sepsis, and septic shock groups were 43.91, 53.75, and 90.70 mg/dl, respectively. We observed that the mean CRP values were significantly higher in more severe cases of sepsis compared to those with less severe illness (Table 1). The sepsis, severe sepsis, and septic shock groups were positively associated with both positive PCT and CRP. However, there was a negative association in SIRS group significantly with PCT ($p=0.013$) than with CRP ($p=0.063$), indicating that PCT is a better marker than CRP to differentiate SIRS from frank sepsis (Table 1).

About 11 patients (18.9%) had PCT <0.5 ng/ml and 22 (41.55%) had PCT >10.0 ng/ml (Table 2). PCT levels of >10 ng/ml were present in a majority of patients in the septic shock and severe sepsis group. PCT positively correlated with CRP in around 38 (84.4%) of children with sepsis ($p=0.029$, Pearson's correlation - 0.589). 10 (18.9%) patients died of their illness; of which, 7 patients (70%) had a serum PCT level of >10 ng/ml (Table 3). This correlation was not observed with CRP levels.

DISCUSSION

Sepsis has so far been diagnosed by collectively reviewing available parameters in the absence of a single, consistent laboratory marker. We have studied PCT levels in these children to assess its role as a single confirmatory marker of sepsis. There was a positive association between serum PCT levels and severe sepsis and septic shock and negative association with SIRS in this study. Sensitivity and positive predictive value

Table 1: PCT and CRP levels

Diagnosis	Number of patients	PCT		CRP	
		Mean PCT values (ng/ml)	Positive n=42 (%)	Mean CRP values (mg/dl)	Positive n=46 (%)
SIRS	9	11.93	4 (44.4)	23.22	6 (66.7)
Sepsis	14	9.63	13 (92.9)	43.91	14 (100)
Severe sepsis	8	17.72	8 (100.0)	53.75	8 (100)
Septic shock	22	84.68	17 (77.3)	90.70	18 (81.8)
Total	53		p=0.013*		p=0.063

PCT: Procalcitonin, SIRS: Systemic inflammatory response syndrome, CRP: C-reactive protein, *: p < 0.05

(PPV) of PCT were high with higher PCT levels in children who died of their illness.

This study, therefore, confirms PCT as a useful inflammatory marker in pediatric sepsis. PCT is the precursor for the hormone calcitonin [8] found in the thyroid C-cells and the pulmonary endocrine cells and is greatly increased in patients with sepsis as a result of hypersecretion from multiple non-endocrine tissues throughout the body. CRP is an acute-phase reactant produced by hepatocytes, triggered by cytokines (IL-1, IL-6, and TNF-α) and its levels increase within 4-6 h of an inflammatory stimulus. Elevations in PCT are generally observed before CRP rises and levels peak within a much shorter time frame. In addition, when the patient responds appropriately to therapy, PCT levels return to normal much quicker than those of CRP. The mean PCT values in the study were found to be elevated in septic shock and severe sepsis compared to SIRS and sepsis. Similar findings were seen in previous studies done by Villon and colleagues [9], and they found that the best markers were serum levels of PCT for the diagnosis of spontaneous bacterial peritonitis at a cut-off value of 0.75 ng/ml with sensitivity of 95% and specificity of 98%.

Fioretto et al., [10] in their study demonstrated that PCT measurement ($p<0.05$) could determine the severity of sepsis at the time of admission and differentiate children with sepsis from those with septic shock. PCT measurement also appears to be more useful in discriminating between sepsis and severe sepsis, in contrast to CRP, blood cell counts or body temperature [11]. In this study, the majority of the patients with septic shock and severe sepsis had PCT levels of >10 ng/ml. The cutoff value of 0.5 ng/ml offered high sensitivity and good PPV in this cohort. Values of 0.5 - 1 ng/ml have shown to be significant in various studies [1,12,13].

The serum values of PCT correlate with the severity of sepsis which decrease with improvement and worsen with exacerbation of the condition. Levels between 0.5 and 2 ng/mL have been labeled the "gray zone" because of difficulties in interpreting the result. Earlier studies have failed [14] to establish a correlation between PCT levels and progression to multiorgan failure. In our study, PCT levels were higher in patients with severe sepsis, but daily PCT assays have not been done to assess the changes in the PCT values with disease progression.

PCT positively correlated with CRP in all groups of sepsis as in earlier studies [15]. However, in our study, PCT values correlated with a diagnosis of SIRS better than CRP. This is helpful to differentiate patients with SIRS from sepsis when signs of sepsis are misleading or absent. Casado-Flores et al., [16] studied 80 children with suspected sepsis and observed that PCT offered better diagnostic and prognostic correlation than CRP, and PCT levels were significantly more elevated among children with septic shock than in sepsis. In a prospective, observational study in children undergoing open heart surgery with cardiopulmonary bypass, PCT was able to differentiate between SIRS and sepsis while CRP could not [17]. Moreover, unlike CRP, PCT concentrations varied with the evolution of disease and as such could also be an indicator of the effectiveness of treatment [18].

In our study, neither leukocyte and platelet counts nor coagulation profile correlated with the severity of sepsis. An earlier study [19] has shown similar results, and they demonstrated that PCT was more useful than CRP, IL-6, and interferon-alpha in the early (within 12 h of illness) detection of invasive infection in febrile infants [20]. PCT has also been shown to indicate the severity of the disease and to be useful in differentiating bacterial from viral infections in children and for making decisions about antimicrobial treatment at the earliest [21]. Mortality was 18.9% in our study with 70% of the children who died having PCT levels of >10 ng/ml. This is similar to an earlier study which has shown that a high PCT level and increase in its level within a day are early independent predictors of mortality [22].

The limitation of our study was that the PCT levels were not serially monitored and not compared with a non-septic control group and hence, changes in the PCT level with the evolution of the disease and treatment could not be firmly established.

Table 2: Diagnostic validity of PCT for predicting sepsis

Biomarkers	Sensitivity	Specificity	PPV	NPV	Accuracy
PCT	86.36	55.56	90.48	45.45	81.13
CRP	90.91	33.33	86.96	42.86	81.13

PCT: Procalcitonin, CRP: C-reactive protein, PPV: Positive predictive value, NPV: Negative predictive value

Table 3: Correlation of PCT values with mortality

PCT	Total number of patients (%)	SIRS (%)	Sepsis (%)	Septic shock (%)	Severe sepsis (%)	Mortality (%)
<0.05	10 (18.9)	5 (55.6)	1 (7.1)	4 (18.2)	0	3 (30.0)
0.05-2.0	7 (13.2)	1 (11.1)	2 (14.3)	3 (13.6)	1 (12.5)	0
2.0-10.0	14 (26.4)	2 (22.2)	7 (50.0)	5 (22.7)	0	0
>10.0	22 (41.5)	1 (11.1)	4 (28.6)	10 (45.5)	7 (87.5)	7 (70.0)
Total	53 (100.0)	9 (100.0)	14 (100.0)	22 (100.0)	8 (100.0)	10 (100.0)

PCT: Procalcitonin, SIRS: Systemic inflammatory response syndrome

Since patients were recruited on admission to the hospital, it is possible that patients would be at differing phases of disease progression on admission, which could also influence PCT levels. However, we tried to minimize this effect by excluding children who were already on antibiotics for >48 h. There was a paucity of positive blood cultures, and clinical diagnostic criteria were used to diagnose and categorize sepsis. The PCT results were blinded to treating physician; treatment was not biased, and the outcome was not influenced by their levels.

CONCLUSION

Our study has clearly shown that PCT levels on admission could differentiate between sepsis and septic shock. PCT levels were found to be higher with increasing severity of sepsis syndromes and in the presence of organ dysfunction/failure, PCT levels also correlated with the mortality. The results suggest that PCT is valid for auxiliary diagnosis of sepsis in children and useful as an indicator of its severity.

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